Isotretinoin–Basal Cell Carcinoma Prevention Trial

Design, Recruitment Results, and Baseline Characteristics of the Trial Participants

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ABSTRACT: The Isotretinoin–Basal Cell Carcinoma Prevention Trial (ISO-BCC Study) is a double-masked, randomized, placebo controlled, multicenter clinical trial. It is the first intramural cancer chemoprevention trial sponsored by the Division of Cancer Prevention and Control of the National Cancer Institute. This trial was designed to evaluate the effectiveness of chronic administration of low dosage levels (10 mg) of a synthetic retinoid, isotretinoin, in reducing the incidence of basal cell carcinoma in a high-risk population and to determine the incidence and severity of side effects associated with this long-term treatment. Between 1984 and 1987, eight clinical centers enrolled 981 participants between the ages of 40 and 75, who had two or more biopsy proven basal cell carcinomas in the 5 years before trial entry. This article describes the trial design, recruitment results, and baseline characteristics of the participant population in the ISO–BCC Study.

KEY WORDS: *chemoprevention, isotretinoin, basal cell carcinoma, design*

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INTRODUCTION

Since 1983, the Division of Cancer Prevention and Control (DCPC) of the National Cancer Institute (NCI) has supported the development of a program of clinical trials in cancer prevention [1]. The aim of these trials includes the reversal of precursor lesions, prevention of the progression from a precursor state to overt malignancy, reduction in the incidence of malignancy, reduction in cancer mortality, and reduction in overall mortality. Treatments under study include the administration of micronutrients as single agents or in combination (beta carotene, vitamins A, C, E, folic acid), dietary changes (low-fat, high-fiber diets) and the administration of synthetic analogs of micronutrients, such as 13-cis-retinoic acid (isotretinoin).

The first intramural trial in DCPC's initial chemoprevention clinical trials program is the Isotretinoin–Basal Cell Carcinoma Prevention Trial or the ISO–BCC Study. In 1982–1983, the scientific concept for the trial was approved by the Division's Board of Scientific Counselors and the protocol was designed by selected intramural staff members from the Cancer Prevention Studies Branch in collaboration with statistical staff from the Surveillance Program (then Biometry and Operations Research Branch), DCPC. The manufacturer of the treatment agent, Hoffmann–LaRoche, collaborated with NCI by providing information vital for the filing of the Investigational New Drug (IND) application and supplying specially manufactured, coded, and labeled isotretinoin capsules and matching placebo capsules free of charge for the trial.

After a pilot study to refine recruitment methods and test the data collection system was conducted, clinical centers were selected and funded through contracts with the NCI. Participant enrollment started in 1984. This article describes the trial design, reports on recruitment results, and presents the baseline characteristics of the study population.

RATIONALE

Basal cell carcinoma is a skin tumor of epithelial origin [2,3]. Each year, 500,000 new cases of nonmelanoma skin cancer develop, with approximately 80% of these being basal cell carcinomas [4,5]. Although mortality directly attributable to basal cell carcinoma is not high, the disease is responsible for considerable morbidity and surgical expense. Current therapeutic modalities involving various forms of surgical excision or ablation have generally yielded cure rates of 95% or higher [4]. However, the expected development of new tumors ranges from 20% in patients with one or more previous basal cell carcinomas to nearly 100% in patients with eight or more previous lesions [6,7]. Thus, the risk of development of new basal cell carcinoma in previously treated individuals can be very high.

Vitamin A and its analogs, collectively known as retinoids, have been actively studied for several years in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease. This vitamin is necessary for the differentiation of epithelial cells and is essential for the development of growth, reproduction, and vision [8].

Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Supplementation with

retinoids can reverse these changes and restore functions of cell growth and differentiation in various cell lines [9–14].

Retinoids administered to animals can prevent chemical carcinogenesis as well. They have been shown to delay the appearance, retard the growth, and cause the regression of cancers of the skin [15], lung or respiratory system [16], urinary tract [17], liver [18], pancreas [19], stomach and cervix [20], and mammary gland [21]. Because in most of the experiments animals were administered retinoids after their exposure to the carcinogen, the prophylactic effect of the retinoids is believed to be in the postinitiation phase, i.e., during promotion of carcinogenesis.

Several epidemiologic studies have also shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin [22–26]. These studies suggest a role for vitamin A intake in the prevention of human malignancies.

The specific effects of retinoids on normal and pathologic skin have long been known, and include alteration of cell maturation, keratinization, sebum excretion [27], and tissue immunity [28]. Successful treatment of Darier's disease, ichthyosis, and conglobate and cystic acne are all based on its pharmacologic effects [29]. Specifically, the efficacy of isotretinoin in these disorders, as well as in the treatment of basal cell carcinoma [30], has been shown. In the latter study, the treatment effect was not striking, with tumor regression occurring in only 9 of 65 lesions. However, during the study and after a 4-year follow-up period, these high risk patients developed no new basal cell carcinomas [31]. Because of this prophylactic effect, it was decided that isotretinoin should be tested in a larger population. It has the advantage of being more effective in skin diseases and shows less systemic toxicity than vitamin A.

In determining the dose of isotretinoin to be used in this trial, the drug's biologic activity (as measured by its effect on sebum excretion rate) [27,32], its side effects and the importance of maintaining the masked nature of the trial were considered. The dose chosen (10 mg/day per patient or approximately 0.14 mg/kg/day for a 70-kg person) was based on information from Hoffmann–LaRoche and a clinical study that showed that isotretinoin exhibits biologic activity in doses as low as 0.1 mg/kg/day [33].

OBJECTIVES

The objectives of this chemoprevention trial are twofold:

1. To evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population; and,
2. To examine possible side effects associated with long term administration of low doses of isotretinoin.

MAJOR DESIGN FEATURES

The major design features are as follows:

- Eight clinical centers located around the United States plus a Data Coordinating Center (DCC) with central quality control measures, including

review of pathology slides of all skin biopsies and verification of clinical center diagnosis.

- Persons of both sexes who are at high risk of developing basal cell carcinoma during the 5-year course of the trial, aged 40–75 years, white, free of serious illness and able to meet other trial eligibility criteria.
- Randomized, double-masked, placebo-controlled trial stratified by clinical center with a sample size of 1000 participants and a treatment period of 3 years during which participants take once daily either 10 mg isotretinoin (two 5-mg capsules) or a matching placebo. Includes a posttreatment follow-up period of 2 years to monitor long-term toxicity that may persist or become manifest after treatment exposure as well as to monitor the effect of discontinuing the treatment on the incidence of basal cell carcinoma.
- A Study Executive Committee that serves as a trial steering committee and is supported by additional specialty committees and an external Data and Safety Monitoring Committee. (The organizational structure is given in the Appendix and Fig. A1).

PATIENT ELIGIBILITY

Each person randomized into the ISO–BCC Study was screened and evaluated to ensure that all eligibility criteria were met and that no medical conditions existed that would exclude the person from participating. In summary, criteria for eligibility and exclusion are as follows:

Criteria for Eligibility

1. Be a white male or female between the ages of 40 and 75.
2. Have had two or more biopsy-proven basal cell carcinomas during the 5 years before randomization.
3. Have normal liver function.
4. Have normal renal function.
5. Give written, informed consent.
6. Be willing and able to participate for the duration of the trial (3 years outpatient treatment, 2 years follow-up).
7. Be willing to seek appropriate definitive treatment for basal cell cancers that arise during the trial.
8. For women, be incapable of childbearing (surgical menopause, tubal ligation at least 1 year prior to randomization, or no menses for at least 1 year).
9. Have entire skin surface evaluable for presence of basal cell carcinoma.
10. Agree not to take high-dose vitamin A (>5,000 U/day) for the duration of the treatment phase of the trial.

CRITERIA FOR EXCLUSION

Criteria for exclusion are based on their ability to interfere with the assessment of trial outcomes (concomitant skin diseases or other topical skin cancer drug treatments), contribute to the potential toxicity of isotretinoin

(presence of hyperlipidemia/hypercholesterolemia), or affect the participant's ability to participate for the 5-year trial (severe coronary artery disease, participation in other studies):

1. Known history of basal cell nevus syndrome, xeroderma pigmentosum, or psoriasis.
2. Use of topical 5-fluorouracil (Efudex) or tretinoin (Retin-A) within 6 months of randomization.
3. Proven active malignancy, other than nonmetastatic basal cell or squamous cell carcinoma of the skin, within 5 years of randomization.
4. Severe coronary artery disease (class III–IV, Criteria of New York Heart Association).
5. Current evidence of hyperlipidemia or hypercholesterolemia.
6. Hypersensitivity to retinoids and/or parabens (preservatives used in the drug capsule shell).
7. Participation in any other studies which may interfere with this trial.
8. Use of isotretinoin within 1 year of randomization.

SCREENING, TREATMENT, AND FOLLOW-UP

Screening Visit

After completing a questionnaire that elicited information on interest in participating in the trial and pertinent medical history, potential participants were seen at a screening visit to determine their eligibility for the trial. At this visit, demographic information was collected, a dermatologic examination performed, fasting blood collected for laboratory determinations, and the informed consent process initiated. Biopsies were taken of suspicious lesions. If eligible, participants returned for a baseline visit within 4 weeks of the screening visit.

Baseline Visit

The baseline evaluation included a physical examination, a dermatologic examination including an assessment of solar damage, a review of laboratory results from the screening visit, and, if necessary, repeat blood determinations of any abnormal screening laboratory tests as well as x-rays of the cervical and thoracic spine. Baseline x-rays are necessary to establish the prevalence of spinal hyperostoses and serve as a reference in screening for retinoid-induced hyperostotic change at the conclusion of the treatment period. This precaution was taken based on a few published case reports [34–38] linking long-term administration of high doses (>1 mg/kg/day) of isotretinoin with spinal changes similar to diffuse idiopathic skeletal hyperostoses [39,40].

A questionnaire designed to elicit physical complaints the person experienced in the year prior to entering the trial was also administered at this visit. The questions were oriented to parts of the body or organ systems that could be affected by the administration of a synthetic retinoid, for example, skin and mucous membranes, and the results serve as a reference in evaluating potential toxicity of isotretinoin at follow-up.

At this visit, biopsies were taken of any additional suspicious skin lesions undetected at the screening visit. If all eligibility criteria were met, persons were randomized and enrolled into the trial. The allocation to trial groups was double-masked and assigned from the Central Data Coordinating Center by telephone after confirming participant eligibility. At the conclusion of the visit, participants were given a supply of study capsules and a health habits–diet history questionnaire to complete and return at the first follow-up visit.

Follow-Up Visits

In order to monitor for skin cancer, potential treatment toxicity, and compliance, randomized trial participants are scheduled to report for follow-up clinic visits at 2 weeks, 3 months, 6 months, 12 months, and every 6 months thereafter for the duration of the trial (3 years treatment, 2 years follow-up). The following procedures are performed at each visit:

- A complete dermatologic examination, including biopsy and removal of all suspicious lesions.
- Collection and testing of blood samples at prescribed intervals to monitor for potential toxicity. Selection and frequency of laboratory tests were based on the expected toxicity profile for isotretinoin (especially changes in serum lipids and liver function tests).
- Administration of a symptoms questionnaire, to elicit information on adverse reactions.
- Pill count and interview to assess participant compliance with the trial medication regimen and to encourage continued compliance or to apply behavioral modification strategies in the noncompliant participant.
- Performance of other follow-up procedures required by the trial protocol (e.g., spinal x-rays; solar damage assessment).
- Documentation of changes in concurrent medication and/or vitamin A usage and hospitalizations or episodes of illness since the last scheduled visit.

DERMATOLOGIC ASSESSMENTS

Trial Outcomes

The number of new basal cell carcinoma (BCC) lesions and the time to first appearance of new BCC lesions are the major outcomes of this trial. The dermatologist-investigators perform a thorough, consistent, and detailed dermatologic examination of the entire skin surface for each participant at each visit. In addition, the dermatologist-investigators take biopsies of any lesion they suspect of being a BCC. The degree of suspicion for the diagnosis of BCC is meant to be high so that early BCCs are not missed. Because the time to appearance of new tumors is a trial outcome, the identification and removal of the tumor at the earliest stage of development is crucial. Definitive treatment and precise recording of the location of lesions are necessary to avoid double counting at follow-up evaluations.

Risk Factors

In the assessment of the incidence of BCC in any population, there must be an evaluation of risk factors for developing new tumors. The major risk factors being considered in this trial include the age of the participant, the number of previous BCCs, the participant's skin type, and the extent of solar damage each participant exhibits. Previous incidence of BCC is probably the most important factor in determining a participant's risk of developing new BCC. For this reason, the number of BCC lesions diagnosed and confirmed by histology in the 5 years before a participant's entry in the ISO–BCC Study was collected at the screening and/or baseline visits. This involved the manual review of all pathology forms for each participant by the study coordinators, reflecting the results of biopsies taken at any institution within 5 years of the participant's entry into the trial.

The participant's skin type, the customary degree of protection from sun exposure (e.g., sunscreens and protective clothing), and whether the participant had had a sunburn in the previous year was also recorded at the baseline visit. The dermatologist-investigators also assessed cumulative solar damage of the participant's skin using a reference set of standardized photographs of sun-exposed parts of the body as a guide, scoring each area using a composite, 7-point scale (range 0 = none, 6 = severe) and entering it on a special data collection form. Evaluation of solar damage is also performed using the same method after 3 years of treatment; this serves to evaluate the amount of interim actinic change incurred by participants during the treatment phase.

TRIAL MEDICATION

Boxes of trial medication containing 400 capsules (4 bottles of 100 each; approximately a 6-month supply) of either isotretinoin capsules (5 mg) or placebo were specially manufactured and supplied by Hoffmann–LaRoche. The small, red, oval, liquid-filled, soft gelatin capsules contain either isotretinoin suspended in soybean oil (active) or soybean oil alone (placebo). The boxes are coded and labeled by participant number and supply A, B, C, D, E, and F (to indicate each of six follow-up visits). They are dispensed sequentially at each 6-month visit over the 36-month treatment period. Individual bottles are labeled as bottle 1 of four, bottle 2 of four, and so on.

STATISTICAL CONSIDERATIONS

Sample Size

The required sample size for this trial was calculated to be 1,000 subjects (500 per treatment group). Calculations were based on the logrank test statistic [41] as well as the usual formula for testing the hypothesis of no difference between two proportions using a uniform 1:1 assignment ratio [42,43]. Time to occurrence of the first new skin cancer (BCC) during the 3-year treatment interval was the primary outcome for the estimation of sample size. The following assumptions were used in the calculation:

1. A 39% annual incidence of new BCC among the placebo treatment group.

This assumption was based on two published studies [6,7], a survey of incident BCCs recorded for patients at a military dermatologic clinic (1980–1983) relating previous BCC tumor formation to subsequent BCC incidence, and the distribution of patients by number of previous BCC.

2. A 20% reduction in BCC incidence at the end of 3 years of treatment in the isotretinoin-treated group compared to the control group.
3. A 35% cumulative noncompliance to treatment regimen in the isotretinoin group (20%, 10%, and 10% per year of treatment, respectively).
4. A 2% cumulative "drop-in" rate (placebo group takes isotretinoin).
5. A 1-year linear lag to intervention effect based on the plausibility that isotretinoin may not be able to affect the occurrence of preexisting, although clinically nondetectable tumors.
6. A 10% loss to follow-up (6% cumulative death rate and 4% lost to follow-up for other reasons).
7. A 90% power and 0.05 two-sided α error.

Analyses for Efficacy

Treatment efficacy is measured by the incidence of new BCC. All primary analyses will follow the "intention to treat principle," i.e., count all outcomes according to participants' originally assigned treatment group. The major analysis will be a comparison of the cumulative incidence curves of first new basal cell carcinoma over the 3-year treatment interval using the logrank two-sample statistic [44] stratified by clinic.

Other important analyses will compare multiple tumors per person developed over the course of the 3 years. Methods used include nonparametric permutation tests based on the randomization distribution to evaluate differences in "occurrence" and "tumor" rates between the two treatment groups, stratified by clinic and number of previous basal cell cancers [45,46]. An "occurrence" rate is defined as the total number of visits at which BCCs are detected divided by the total duration of follow-up for all individuals (person-years) and a "tumor" rate is the total number of BCCs for all visits divided by the person-years.

Statistical approaches based on regression models will also be used to compare differences in tumor and occurrence rates between the treatment groups. One approach is based on repeated measures interval count data using Poisson regression models [47] in which the number of tumors for each individual occurring within a time interval is described by a time function for the "tumor" rate, covariates related to this rate, and an individual effect. A second approach, longitudinal logistic time-dependent covariate regression models [48], will be used to explore interpretation of "occurrence" rates in which the time-dependent covariate is the cumulative number of prior BCCs since baseline. Non-time-dependent covariates for both models will include prior BCCs at baseline, clinic, sex, age, solar damage, and dietary factors. Interactions will be investigated such as those between treatment and follow-up time, treatment and number of prior BCCs at baseline, and treatment and diet.

Other outcomes will include squamous cell cancer and histologic subtypes of basal cell cancers (multicentric versus other). Dose–response analyses will

also be examined. The two years of follow-up after the 3 years of treatment will be analyzed by methods similar to those described above.

Interim Analyses

A group sequential monitoring procedure for the logrank statistic assessing efficacy in terms of time to first tumor is used in conjunction with semiannual meetings of the trial's Data and Safety Monitoring Committee [49–51]. This procedure allows for interpretation of statistical significance if an effect is observed earlier and/or is larger than expected, without the repeated significance testing jeopardizing (increasing) the final alpha error. Conservative O'Brien–Fleming type boundaries were specified for the early interim analyses because the evidence of efficacy must be substantial to influence revision of the original trial design. Moreover, the conservative criteria also reflect the conjectured delay (lag) to effect and the desire not to jeopardize another primary study goal, monitoring of potential long-term toxicity of isotretinoin. Evidence of unacceptable toxicity at any time could also lead to a recommendation for early discontinuation of the treatment period.

ORGANIZATION

The major groups in the administrative structure of the trial include the Study Chairman, the Study Group, the Study Executive Committee, the Editorial Committee, and the Data and Safety Monitoring Committee.

Study Chairman

The Study Chairman is responsible for general coordination and oversight of the trial, including allocation of funds and distribution of appropriate reports and relevant data to each committee. He chairs the Study Group and the Study Executive Committee, and monitors and evaluates each clinical center's technical performance for the duration of the trial.

Study Group

The Study Group includes all participating investigators, study coordinators, and permanent consultants to the trial. The group meets every 6–12 months to discuss trial progress and solve problems encountered by investigators. Appropriate recommendations on changes and improvements are made to the study Executive Committee. This group remains masked to treatment allocation until the trial is completed.

Study Executive Committee

The Study Executive Committee is made up of the Study Chairman, staff members from the Data Coordinating Center, investigators from the Prevention Research and Surveillance Programs of DCPC and the Senior Dermatologist consultant. This committee serves as the major decision-making body

for the operational aspects of the trial and provides overall scientific direction for the trial. This committee does not have access to any unmasked data but does act on the recommendation made by the Data and Safety Monitoring Committee.

Data and Safety Monitoring Committee

The data and safety monitoring functions for the trial are regularly performed by a panel recruited from outside the Prevention Research Program, DCPC. Committee members include a dermatologist, a statistician, and a physician with experience in monitoring large multicentered clinical trials. The committee meets twice yearly during the trial to review tabulated aggregate toxicity and outcome data provided by the Data Coordinating center. They submit written recommendations on the progress of the trial to the Study Executive Committee.

RECRUITMENT AND PATIENT ENROLLMENT

Participants entered the trial primarily through one of three mechanisms:

1. Some were identified as potentially eligible through investigator-initiated review of the clinical center's medical records and/or pathology logs.
2. Some were seen during a routine dermatology clinic visit and were found to have two or more new BCCs, or were found to have one lesion in addition to having had at least one previous BCC within 5 years before the visit.
3. Some were referred from private dermatologists or other medical specialists outside the Dermatology Clinic.

Sixty-nine percent of the participants randomized were initially identified from the Dermatology Clinic pathology logs, which listed patients with pathologically confirmed basal cell carcinoma in the 5 years before trial start-up. These names were linked to the patient medical records, which were preliminarily reviewed for major eligibility criteria (white male or female, 40–75 years old, two or more biopsy-proven BCCs during the previous 5 years). Patients who met these preliminary criteria were called, asked if they were interested in participating, and scheduled for a screening clinic visit. If patients could not be reached by phone easily, they were sent a questionnaire designed to elicit further information on interest in participating and potential eligibility (includes question on age, sex, brief medical history, etc.). A patient brochure that outlined the purpose and components of the trial in layman's terms was also sent. Interested and eligible patients were scheduled for a screening visit. Forty-three percent of persons to whom this questionnaire was sent indicated they were interested in participating and potentially eligible for randomization in the trial, 26% had no interest in the trial, 9% could not be contacted, and 22% were ineligible on the basis of a review of the questionnaire response. Overall, one of five patients contacted, either through clinic visit or questionnaire, was ultimately randomized and enrolled as a trial participant.

The majority of trial participants came from the active dermatology clinic

patient population at each of the eight clinical centers. This proved to be advantageous since these participants, by nature of their prior incidence of skin cancer, were accustomed to returning to the clinic once or twice annually to be checked for new lesions. In most cases, they already had an established doctor–patient relationship with the dermatologist-investigator. It is not surprising that participant compliance with the follow-up visits required by the protocol has currently exceeded 95%.

Accrual of eligible participants was a long and arduous process. The trial was started with five military clinics serving as clinical centers and a planned recruitment period of 18 months. Military dermatology clinics were initially chosen for study centers due to their large population of retired military personnel and dependents routinely treated for recurrent BCC. It was initially planned to conduct the trial at eight military centers, but three withdrew from consideration prior to award due to work load and staffing problems. Because the five military centers funded could not make up the accrual lag and meet recruitment goals in a reasonable period of time, it was decided to advertise a request for proposals from the general public. This resulted in the funding of three private sector facilities in 1986. The addition of the three private centers bolstered lagging accrual greatly, with enrollment of over 350 participants in about 18 months. By spring of 1987, it was evident that the population of potential trial participants was exhausted and the initial accrual goal of 1000 participants could not be reached without extending an already lengthy accrual period. A common date for the close of the accrual phase was set for June 1987, at which time 981 participants were enrolled (Table 1).

BASELINE CHARACTERISTICS

Baseline characteristics that serve as key study covariates are presented by treatment group in Table 2. All observed differences in Table 2 occurred by chance due to randomization.

Demographic Data

Nonmelanocytic skin cancer (BCC and squamous cell carcinoma) is due, for the most part, to the cumulative effects of ultraviolet radiation on the skin. The incidence increases with age, with the greatest percentage of skin cancer

Table 1 Annual Participant Accrual by Clinical Center

Clinical Center	1984	1985	1986	1987	Total
Brooke Army Medical Center	46	57	39	25	**167**
Walter Reed Army Medical Center	18	43	47	25	**133**
Portsmouth Naval Hospital	28	46	22	8	**104**
Fitzsimons Army Medical Center	16	40	28	14	**98**
Eisenhower Army Medical Center	—	65	40	22	**127**
Northwestern University	—	—	108	43	**151**
University of Arkansas	—	—	100	25	**125**
Roswell Park Memorial Institute	—	—	57	19	**76**
					981

Table 2 Baseline Characteristics of Trial Participants

Characteristic	Group A (n = 490)	Group B (n = 491)
Mean age (yr)		
Overall	60.9	60.7
Men	61.6	62.1
Women	60.2	59.3
Previous basal cell carcinoma[a]		
2 tumors	37.4%	38.3%
3–4 tumors	33.5%	35.2%
>4 tumors	29.0%	25.7%
Skin type (Fitzpatrick score)	2.1	2.2
Overall solar damage grade	2.7	2.8
Skin protection used		
Sunscreen use	51.7%	50.5%
Protective clothing	59.5%	63.4%
Sun avoidance	43.8%	44.8%
Vitamin supplement use	39%	33%

[a]Histologically proven basal cell carcinoma occurring in 5 years before trial entry.

occurring in those 40 years of age and older. Therefore, the acceptable age range for trial entry was set at 40–75 years. The average age of trial participants is about 60 years, with males being slightly older than females. The male-to-female ratio for trial participants was about 4:1. Additional demographic information was collected from participants using a health habits and history questionnaire [52].

Physical Findings

Physical complaints experienced by the patient in the year before entering the trial were elicited at the baseline visit using a symptoms questionnaire. The most common baseline symptom reported by the trial participants was mild or moderate pain or stiffness in the joints or back (75%), followed by dry skin on the body (58%) and chapped lips (47%). This array of physical complaints is expected in an older population.

History of Skin Cancer

As previously described, the study coordinators reviewed the patient's medical records and obtained official copies of the pathology reports for all BCC and squamous cell carcinomas of the skin. Almost two thirds (62%) of the participants had three or more BCCs in the 5 years before trial entry (Table 2). Fourteen percent of the trial population had one or more squamous cell carcinomas of the skin in the 5 years before randomization.

Solar Damage Assessment

At the baseline visit, the dermatologist-investigators assessed cumulative solar damage of each participant's skin using a reference set of standardized photographs of sun-exposed parts of the body as a guide, as described pre-

viously. The average grade for the six areas scored by the dermatologist investigator for each participant was 2.7 (range 0.3–5.3) (Table 2), indicating that this trial population exhibited a moderate amount of actinic damage at baseline. Based on the high number of prior BCCs in this population, one would have expected a greater degree of actinic damage. These results do not fit well with the accepted profile of a skin cancer patient (fair skin, extensive actinic damage) and could be an indication that the method used to assess solar damage was not applied properly or was incorrectly constructed. It could also mean that the accepted profile is an incorrect overgeneralization, that is, one does not need to incur severe sunlight damage to the skin to develop BCC.

Skin Type and Sun Protection Methods

The dermatologist-investigator assessed each participant's skin type using the standard series of questions used in Fitzpatrick skin grading [53] and by noting the participant's eye color, hair color, and skin color in body areas not exposed to the sun. As expected in this population of nonmelanocytic skin cancer patients with a prior history of multiple skin lesions, most are fair skinned, with an average Fitzpatrick skin type grade of 2.1. Sun protection methods were determined by questionnaire, which included questions on sun avoidance, use of protective clothing, and use of sunscreen or sunblock. About half of the participants used one or more methods "frequently or always" and more than 75% used one or more methods of sun protection at least "sometimes." These questions were not meant to be mutually exclusive and most participants used a combination of sun avoidance and sun protection to prevent further actinic damage to the skin (Table 2).

CONCLUSION

At present (June 1990), the planned 3-year treatment phase of the trial has ended. All participants are currently in the off-treatment follow-up phase. Compliance with the protocol and treatment regimen has been uniformly excellent, with almost 90% of trial participants taking greater than 90% of the prescribed treatment regimen and more then 95% of participants complying with the protocol visit schedule. The trial participant dropout and loss to follow-up rate has been lower than expected. Results of the 3-year treatment phase of the trial will be available for publication in early 1991. Trial participants will continue to be followed off-treatment until August 1991, the common closeout date for all clinical centers.

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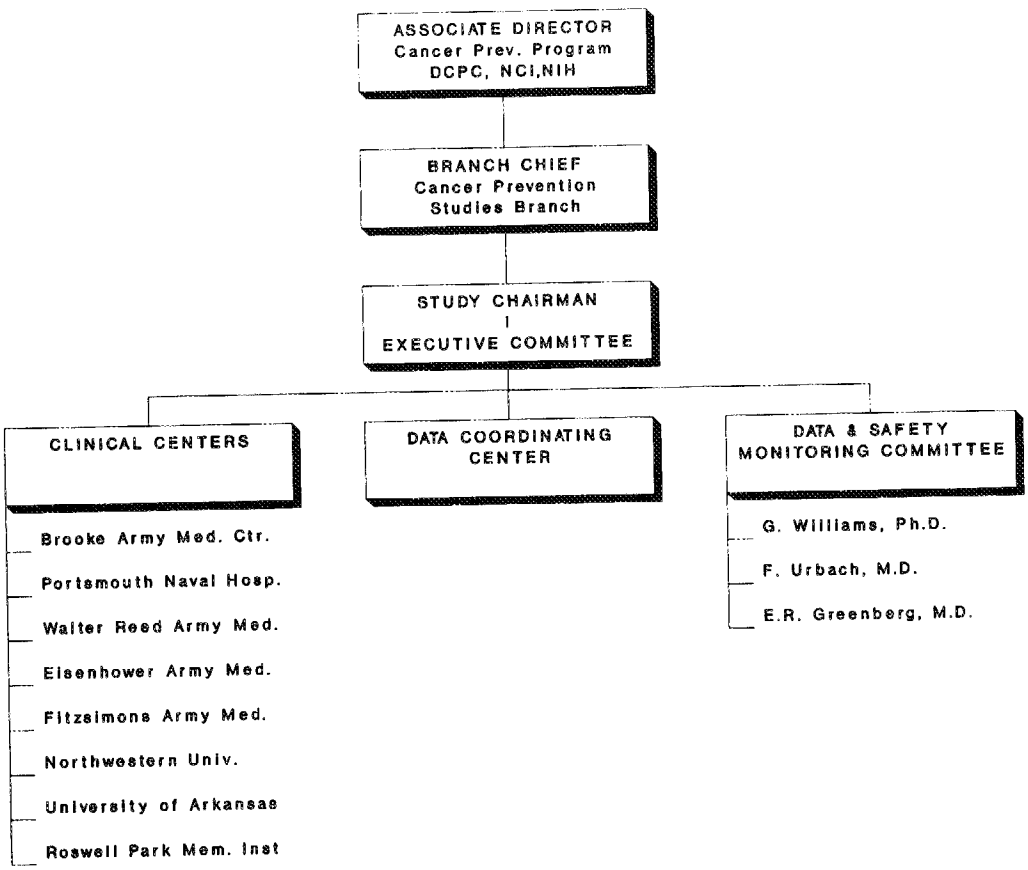

Figure A1 I SO-BCC Study organization

APPENDIX: ISO-BCC Study Group

a. Study Executive Committee

Joseph Tangrea, RPh, MPH, Study Chairman
Brenda Edwards, PhD
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b. Data Coordinating Center

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William Helsel, MS
Maria Elena Adrianza, BA
Hyun-Sook Lee, BS (1984–1986)

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Christine Rohrbacher, RN (1984–1987)

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James Aton, MD

Study Coordinator: Pat Challenger, RN

Fitzsimons Army Medical Center

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Study Coordinators: Leslie Perlman, BS
Janice Jurumbo, RN (1985–1987)

Roswell Park Memorial Institute

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Connie Jones, MD

Study Coordinator: Barbara Slusarski, RN, MS

d. Study Consultants

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Marc Micozzi, MD

Central Radiologists: Roberta Helfgott, MD
Ray Kilcoyne, MD

Pharmaceutical Liaison: Loretta Itri, MD
Robert Dennin
Hoffman–LaRoche, Inc.

e. Data and Safety Monitoring Committee

Fredrick Urbach, MD, Chairman
E. Robert Greenberg, MD
George Williams, PhD